REMARKS

Claims 8 and 17-23 are pending. Claims 8, 17 and 23 are newly amended. Claims 24-26 are newly added. Support for the amendment is found throughout the specification and claims as originally filed and is discussed further below. No new matter has been entered.

Specifically, support for the newly added claim limitation of measuring regulatory T cell responses in claim 8 and dependent claims includes:

> "Dosage of a parasite preparation may be monitored by measuring Th1, Th2 or regulatory cell responses", paragraph 163 of the instant specification.

and paragraphs 169-172 of the published specification:

"Regulatory T cell response or activity may be measured by an internal marker, a cell surface marker, or a secreted marker as described herein", [0169]

"Useful internal markers for regulatory T cells include, but are not limited to, transcription factors such as Scurfin, Smad7, Gata3, Tbet (Tbx21)", [0170].

"Useful surface markers for regulatory T cells include, but are not limited to, CD4, CD45RB.sup.lo, CD45Rc, Cytolytic T lymphocyte associated antigen 4 (CTLA-4), CD25, CD103, Ox40, 4-1BB, CD62L, $\alpha\varepsilon\beta$ integrin, latency-associated peptide (LAP) or glucocorticoid induced TNF receptor family related protein (GITR), chemokine receptor CCR5, TI-ST2", [0171].

and

"Useful secreted markers for regulatory T cells include, but are not limited to, IL-5, IL-10 and TGFβ", [0172]

Support for newly added claims 23-26 includes:

> "As used herein, the term "regulatory T cells" refers to a lymphocyte cell population which secretes at least 2-fold increase (e.g., 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold or more) of IL-10 and/or TGFβ, as compared to nave T cells", paragraph 47 of instant specification as published
>
> and
>
> "Optionally, the regulatory T cells may also make much less IFNγ as compared to other T cells (e.g., nave T cells), i.e., at least 2-fold, preferably 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 10-fold or less", paragraph 47 of instant specification as published

35 U.S.C. § 102(b)

The rejection of Claims 8, 17-18, 20 and 22-23 is maintained under 35 U.S.C. 102(b) as being anticipated by Weinstock et al. (WO 99/33479).

Anticipation requires that the purported prior art reference disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO incorporated et al.,* 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Applicant respectfully traverses on the grounds that all the limitations of the instantly claimed method as newly amended are not taught by the cited reference of Weinstock et al. (WO 99/33479). The claims include a method step comprising measuring regulatory T cell responses, a method step not taught by Weinstock et al.

Applicant disagrees with the position of the Examiner that Weinstock et al. anticipates the instant claims by their determination of the presence of Th1 and Th2 responses after treatment with the claimed composition in order to show efficacy of their method, page 3 of the office action dated 5/22/09. Applicant notes that determination of Th1 and Th2 responses is distinct from the instantly recited step of measuring regulatory T

cell responses. That is, a determination of a Th1 and Th2 response is not equivalent to measuring regulatory T cell responses, as required by the instant claims.

The Office Action concludes Weinstock et al. is anticipatory because it discloses the Th1 and Th2 responses were determined by measuring the production of various cytokines and cell surface markers including IL4, IL-5, TGFβ and IFNγ, pages 3-4 of the office action dated 5/22/09. Applicant submits that even if some cytokine markers of Th1 and Th2 responses overlap with cytokine markers of regulatory T cell responses, the overlap does not render Weinstock et al. anticipatory since two separate entities (Th1/Th2 responses vs. regulatory T cell responses) are being measured by these overlapping cytokine markers. A measurement of a level of a single cytokine has different meanings with respect to the measurement of a Th1 response, a Th2 response or a regulatory T cell response.

The specification of Weinstock et al. does not teach how to correlate a cytokine level with measuring regulatory T cell responses. Thus, Weinstock et al. does not teach how to measure a regulatory T cell response, despite its teaching the measurement of cytokines to measure a Th1 response or a Th2 response. Because Weinstock et al. does not disclose the step of measuring regulatory T cell responses by measuring a level of a regulatory T cell marker, as required by the instant claims, Applicant submits that Weinstock et al. is not anticipatory.

The instant claims as newly amended are drawn to a method for treating an animal with a Th1 or Th2 related disease comprising administering to the animal a helminthic parasite preparation that alters a regulatory T cell activity; and measuring regulatory T cell responses.

In contrast to measuring regulatory T cell responses, as required by the instant claims as newly amended, the cited art, Weinstock et al., teaches assessing the presence of a Th1 or a Th2 response, after administering a helminthic parasite preparation. Weinstock et al. does not mention T regulatory cells, nor the cytokines they secrete, nor

their distinguishing cell markers, nor their activity, all of which are encompassed by the instant claims.

Weinstock et al. discloses methods of treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation. Weinstock et al. discloses the determination of Th1 and Th2 responses by measuring the production of various cytokines and cell surface markers after administering a helminthic parasite preparation in order to show efficacy of the treatment. Specifically, in section D, entitled "Determination of Th1 and Th2 responses", Weinstock et al. discloses:

> " In order to show the efficacy of the present invention, the Th1 and Th2 response must be distinguished. Metawali et al., 1996, J. of Immunol. 157:4546 has shown that in mice, it is possible to distinguish a Th1 from a Th2 response by histologic analysis, and by analysis of cytokine and immunoglobulin profiles. Further, Sandor et al., 1990, J. of Exp. Med-171:2171 has shown that cell surface expression of Fcγ3 and MHC Class II molecules afford discrimination. In this procedure, small bowel and colon are examined histologically to determine the degree of mucosal inflammation, eosinophilia and mastocytosis. The latter cell types are indicative of a Th2 response. Mesenteric lymph nodes (MLN) and spleens can be dissociated into single cell suspensions for in vitro culture in microwell plates. Cells (1-2 x 10^7/well) in complete RPMI medium are cultured for up to 72 h in the presence or absence of worm antigen or anti-CD3 and then the supernatants are assayed for cytokines and immunoglobulins. IFN-γ, TNFα and IgG2a characterize a Th1 response, whereas IL-4, IL-5, IgE and IgG1 typify a Th2 reaction. Also, serum can be assayed for cytokine and immunoglobulin concentrations. Furthermore, dispersed inflammatory leukocytes are examined by flow cytometry for Fcγ3 expression on macrophages (Th1) and MHC Class II expression on B cells (Th2). Controls include serum, MLN and spleens from appropriate age-matched, littermate mice that hosted no parasite. Also, there are other markers of the Th1 vs. Th2 responses", emphasis added, pages 21-22 of the instant specification.

In contrast to Weinstock et al., which looks at Th1 and/or Th2 cell activity, the instantly claimed invention is directed to a method directed at measuring regulatory T cell

responses. This distinction is illustrated in the first sentence of the instant "Summary of the Invention" which states:

> " The present invention is based on the finding that parasite preparation can alter the activity of regulatory T cells in the treatment of Th1 or Th2 related disease", emphasis added, page 4 of the instant specification.

Thus, the focus of the instantly claimed methods is on markers and cytokines of T regulatory T cells, as opposed to markers and cytokines of Th1 T cells and/or Th2 T cells as taught by Weinstock et al.

As disclosed in the specification, T regulatory cells regulate Th1 and Th2 cells.

> " These regulatory T cells (Tr cells) express a transmembrane protein (called CD25) that is alpha chain of the receptor for interleukin-2 (IL-2). Like other T cells, they also express the αβ (alpha-beta) T-cell receptor for antigen (TCR) and can only be activated if it binds to the peptide-class II MHC molecule, or in the case of CD8 regulatory cells Class I MHC, for which it is specific. However, if activated, they begin to secrete large amounts of interleukin 10 (IL-10) and often some transforming growth factor-beta (TGF-β) as well. Both these lymphokines are powerful immunosuppressants inhibiting Th1 help for cell-mediated immunity and inflammation, Th2 help for antibody production, and, possibly, the action of $CD8^+$ cytolytic T lymphocytes (CTL)", emphasis added, page 4 of the instant specification.

The instant specification teaches that only regulatory T cells are known to express *Foxp3,* page 66, line 21, and further discloses that markers of these regulatory T cells include secretion of increased amounts of IL-10 and/or TGFβ, decreased amounts of IFNγ, and expression of a high level of Foxp3 transcript, and its protein product Scurfin:

> "... the term "regulatory T cells" refers to a lymphocyte cell population which secretes at least 2-fold increase (e.g., 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold or more) of IL-10 and/or TGFβ, as compared to nave T cells. The determination of IL-10 or TGFβ secretion is known in the art. For example, it may be

> determined by culturing the cells *in vitro* for 24 or 48 with or without a T cell stimulant like anti-CD3 and then assaying the culture supernatant for these cytokines using cytokine specific ELISAs. In addition, regulatory T cells of the present invention is also characterized by a high level of FoxP3 transcript as compared to other types of T cells (e.g., naive T cells). ... Alternatively, FoxP3 protein product, Scurfin, can be detected by Western blotting analysis as known in the art, e.g., using Goat Anti-FoxP 3 (FoxP3) Polyclonal Antibody (Catalog Number ab248 1, Novus Biologicals, Littleton, Colo.). Optionally, the regulatory T cells may also make much less IFNγ as compared to other T cells (e.g., nave T cells), i.e., at least 2-fold, preferably 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 10-fold or less. Also optionally, regulatory T cells also can be detected by using intracytoplasmic flow analysis to detect T cells expressing IL10 and/or TGFβ but little or no IFNγ. Additional optional markers as described herein below may also be used for detecting regulatory T cells or the activity of regulatory T cells", emphasis added, pages 10-11 of the instant specification.

Thus, the instant claims for treating a Th1 or Th2 related disease with a helminthic preparation comprise measuring regulatory T cell responses, a limitation not taught by Weinstock et al. Weinstock et al. teaches methods of assessing Th1 and/or Th2 cell activity, but does not teach a method comprising the step of measuring regulatory T cell responses, as required by the instant claims. Specifically, Weinstock et al. does not teach a method encompassing the steps of measuring regulatory T cell responses by analyzing expression of individual markers and/or cytokines, e.g., FoxP3, CD25, or a combination of markers and/or cytokines, in order to measure regulatory T cell responses, as required by the instant claims.

Applicant respectfully disagrees with the position of the Office Action on page 3, that Weinstock et al. is anticipatory. The Office Action justifies the position by noting that the specification discloses that the activity of regulatory T cells can be determined with IL-4, IL-5, TGFβ and IFNγ; as follows:

> "given that Weinstock et al. disclose the determination of Th1 and Th2 responses after treatment with the claimed composition 'in order to show the efficacy' of their method (see page 21), and said responses

> were determined by measuring the production of various cytokines and cell surface markers including IL-4, IL-5, TGFβ and IFNγ, (see pages 21-25) Weinstock et al. anticipates the instant claims", pages 3-4 of the Office Action dated 5/22/09.

As acknowledged by the Office Action in the above excerpt, Weinstock et al. is looking at Th1 and Th2 cells, not the T regulatory cells of the instant claims. Applicant notes that measuring the Th1 Th2 response is one way of determining the efficacy of the method, as disclosed in the instant specification:

> "In order to show the efficacy of the present invention, the Th1 and Th2 response may be distinguished. Metawali et al., 1996, J. of Immunol. 157:4546 has shown that in mice, it is possible to distinguish a Th1 from a Th2 response by histologic analysis, and by analysis of cytokine and immunoglobulin profiles", paragraph 165 of the instant specification.

However, Applicant notes that the efficacy of the method, (including the dosage of parasite used in the method) can also be assessed by measuring regulatory T cells, as well as by measuring TH1 and/or Th2 responses. .

> "Dosage of a parasite preparation may be monitored by measuring Th1, Th2 or regulatory cell responses", paragraph 163 of the instant specification.

Applicant further notes that Weinstock et al. does not teach measuring regulatory T cell responses, as required by the instant claims and disclosed in the instant specification:

> "The activity of regulatory T cell may be measured by monitoring the level of a regulatory T cell internal marker (e.g., a transcription factor such as FoxP3 mRNA or its protein product Scurfin, Smad7, Gata3, or Tbet (Tbx21)), or a regulatory T cell surface marker (e.g., CD4, CD45RB.sup.lo, CD45Rc, Cytolytic T lymphocyte associated antigen 4 (CTLA-4), Ox40, 4-1BB, CD25, CD103, CD62L, $\alpha_E\beta$ integrin, latency-associated peptide (LAP) or glucocorticoid induced TNF receptor family related protein (GITR), Experimental allergic encephalitis (EAE), chemokine receptor CCR5, TI-ST2) or a secreted marker (e.g., IL4, IL13, IL-5, IL-10, TGFβ). An increased regulatory T cell activity may

be represented by an increase (e.g., FoxP3, Ox40, 4-1BB, CD4, CTLA-4, CD25, CD103, CD62L, $\alpha_E\beta$ integrin` LAP, GITR, EAE, CCR5, TI-ST2, IL-10, TGFβ)..", pg 11, lines 20-29 of the instant specification.

That is, unlike the instant claims and specification, Weinstock et al. is not measuring regulatory T cell responses when determining a cytokine level, including the level of one or more of the following cytokines: IL-4, IL-13, IL-5, IL-10, to determine Th1 or Th2 activity. Further, Weinstock et al. does not disclose measuring the non-cytokine markers recited in pending claims 18-22. Because Weinstock et al. does not teach measuring regulatory T cell responses, nor markers thereof, Weinstock et al. is not an anticipatory reference.

Because WO 99/33479 does not teach a method comprising determining the measuring regulatory T cell responses as required by the instant claims, Applicant respectfully submits that WO 99/33479 is not prior art, and accordingly does not anticipate the instant claims.

35 U.S.C. § 103(a)

Claims 8 and 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al (WO 99/33479).

Applicant respectively traverses.

Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), recently reaffirmed by *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), provides the analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis.

Moreover, to establish a prima facie obviousness rejection of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Predictability is required in maintaining a legal conclusion of obviousness under both KSR and the USPTO published guidelines.

Independent Claim 8, as newly amended, is drawn to a method for treating an animal with a Th1 or Th2 related disease comprising administering a helminthic parasite preparation that alters a regulatory T cell activity to said animal; and measuring regulatory T cell responses.

As discussed in the above rebuttal to the 102 rejection, Weinstock et al. do not teach all the limitations of the claims as newly amended, in particular the recited limitation of measuring regulatory T cell responses. Weinstock et al. does not teach measuring regulatory T cell responses.

The Office Action indicates that it would have been obvious for the skilled artisan to use the regulatory T cell markers recited in claims 19 and 21 in the methods of Weinstock et al. "for determination of Th1 and Th2 responses after treatment with the claimed composition 'in order to show efficacy of their method' " "since the use of screening of the recited T cell activation markers is well known in the art", emphasis added. However, the Office Action provides no explanation of how the phrase "T cell activation markers" relates to the instantly claimed method comprising measuring regulatory T cell responses, nor how "T cell activation markers" relates to markers used to measure regulatory T cell responses as recited in the instant dependent claims.

The office action states on page 6 that "with regards to the role [regulatory T cells?] actually plays in the treatment process merely constitutes a further characterization of a known methods". Applicant respectfully disagrees with this statement since absent objective evidence, the second step of the claimed method – that of measuring regulatory

T cell responses after administering a helminthic preparation, was not known. Further, nowhere in the motivation of the office action, nor in the cited art, is there provided a reason to look at markers of T regulatory cells, in the claimed method of administering a helminthic parasite preparation, including those recited in the instant dependent claims. Thus, the instant claims are not a further characterization of a known method, but provides a means, in one embodiment to monitor the effectiveness of the administered dose.

Recent case law dictates that a finding of obviousness requires that the prior art provide evidence that that the suggestion would be successful. In re Kubin, 2008-1184 (Fed. Cir. April 3, 2009)(Serial No. 09/667,859) quotes O'Farrell (853 F.2d. 894, 903 (Fed. Cir. 1988), adding emphasis to the phrase "detailed enabling methodology" by underlining it

> "specifically this court observed that an obviousness finding was appropriate where the prior art contained a detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention and evidence suggesting that it would be successful." 853 F.2d at 902 .

In the absence of documentary prior art providing a disclosure that measuring regulatory T cell responses would be applicable in a method for treating an animal with a Th1 or Th2 related disease, as encompassed by the instantly claimed methods, Applicants respectfully submits that one of skill at the time of the invention would not have had a reasonable expectation of success in practicing the methods of the instant claims, e.g., for example in monitoring dosage.

As described above, Weinstock et al. discloses methods of treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation. Weinstock et al. discloses the determination of Th1 and Th2 responses by measuring the production of various cytokines and cell surface markers after administering a helminthic parasite preparation in order to show efficacy of the treatment.

However, as also described above, WO 99/33479 does not teach a method comprising measuring regulatory T cell responses as required by the instant claims.

Further, the instant specification discloses that at the time of the invention, the role of regulatory cells in a treatment comprising the administration of a helminthic preparation for a disease with an aberrant Th1 response was not known.

> " It remains unknown whether regulatory T cells play a role in the prevention or treatment of Th1 or Th2 related diseases using a helminthic parasite preparation", page 4, lines 20-21.

As discussed above, predictability is required in maintaining a legal conclusion of obviousness under both KSR and the USPTO published guidelines. However, the office action provides no grounds on which one of skill could predictably ascertain that regulatory T cells play a role in the treatment of Th1 or Th2 related diseases comprising administering a helminthic parasite preparation.

The Office Action indicates that the use of screening of the recited T cell activation markers is well known in the art. However, the instant claims are not drawn to a method of treatment comprising determining the level of T cell activation markers. Instead, the instant claims are drawn to a method of treatment comprising measuring regulatory T cell responses by determining in some embodiments the level of regulatory T cell markers.

Therefore, without the benefit of Applicant's specification, one of skill could not have reliably predicted a method that encompassed measuring regulatory T cell responses in the treatment of Th1 or Th2 related diseases after the administration of a helminthic parasite preparation. Without evidence that one of skill in the art could have predictably arrived at the claimed invention based on the teachings of Weinstock et al., and not based on the teachings of the instant specification, a prima facie case of obviousness under KSR has not been achieved.

Conclusion

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney's/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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